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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/788,489	03/01/2004	Serge Carillo	ST94037B	9027

29693 7590 04/30/2008

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EXAMINER	
LONG, SCOTT	

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
04/30/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/788,489	CARILLO ET AL.	
	Examiner	Art Unit	
	Scott D. Long	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/405920.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/19/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner acknowledges receipt of Applicant's Remarks and Claim amendments, filed on 19 February 2008.

Claim Status

Claims 1-8 are pending. Claims 1-2 and 5 are amended. Claims 1-8 are under current examination.

Information Disclosure Statement

The Information Disclosure Statements (IDS) filed on 19 February 2008 consisting of 5 sheet(s) are in compliance with 37 CFR 1.97. Accordingly, examiner has considered the Information Disclosure Statements.

Priority

This application claims benefit as DIV of 09/405,920 (filed 09/24/1999 ABN) which is a CON of 08/737,953 (filed 11/27/1996 ABN) which is a 371 of PCT/FR95/00670 (filed 05/22/1995). The application also claims benefit from foreign application, FRANCE FR94/06583 (filed 05/31/1994). The instant application has been granted the benefit date, 31 May 1994, from the application FRANCE FR94/06583.

Response to Arguments - Claim Rejections 35 USC § 112

Response to Arguments – 35 USC 112, second paragraph

Applicant's arguments, see page 5-6 and Claim amendments, filed 19 February 2008, with respect to claims 2 and 5-7 have been fully considered and are persuasive. The rejections of Claims 2 and 5-7 under 35 USC 112, second paragraph, has been made moot by the claim amendments submitted on 19 February 2008 and are hereby withdrawn.

Response to Arguments – Written Description (35 USC 112, first paragraph)

The examiner withdraws the rejection of claims 5 and 7 under 35 U.S.C. 112, first paragraph (written description).

Applicant's arguments (Remarks, pages 5-6) filed 19 February 2008 have been fully considered and they are persuasive.

The applicant argues that "with respect to the structure of calpastatin referred to in the Office Action at page 5, the Carafoli review document, of record in this and parent case, refers to several documents at page 194 (reference numbers 32-34) that indicate that one of skill in the art did indeed possess information on the inhibitory domains in the calpastatin protein." (Remarks, page 6).

After reviewing Carafoli et al. (Biochemical and Biophysical Research Communications, 1998; 247: 193-203), the examiner has concluded that the prior art

does identify with sufficient clarity, that specific domains of the calpastatin protein which are responsible for inhibiting protease activity of calpain. However, there is no indication in Carafoli et al., that "fragments of the calpastatin protein" are capable of inhibiting protease activity of calpain. Therefore, the examiner finds Carafoli et al. insufficient to overcome the examiner's rejection that the applicant was not in possession of fragments of calpastatin which are inhibitors of calpain protease activity. In addition, Carafoli et al. was published after the filing of application FRANCE FR94/06583 and would not have been available to a skilled artisan at the time of filing.

However, the prior art does indicate that some fragments of calpastatin were known to inhibit calpain protease activity. See Henkart et al. (US-5,607,831, issued 4 Mar 1997) and Maki et al. (The Journal of Biological Chemistry, Nov.15, 1989; 264(32): 18866-18869). Therefore, the examiner accepts the rationale provided by the applicant, but prefers to rely on different references to base his decision to withdraw the pending rejection.

Therefore, the examiner hereby withdraws the rejection of claims 5 and 7 under 35 USC 112, first paragraph (written description).

Response to Arguments - Claim Rejections 35 USC § 102

Claims 1-2 and 8 rejected under 35 U.S.C. 102(b) as anticipated by Ramsby et al. are withdrawn in response to the applicant's claim amendments.

Applicant's arguments (Remarks, pages 6-7) filed 19 February 2008 have been fully considered and they are persuasive.

Therefore, the rejection of claims 1-2 and 8 rejected under 35 U.S.C. 102(b) as anticipated by Ramsby et al. (Electrophoresis. 1994 Feb;15(2):265-277) is hereby withdrawn.

Response to Arguments - Claim Rejections 35 USC § 103

Claims 1-8 rejected under 35 U.S.C. 103(a) as obvious over Ramsby et al. in view of Asada et al. are withdrawn in response to the applicant's claim amendments.

Applicant's arguments (Remarks, pages 8-10) filed 19 February 2008 have been fully considered and they are persuasive.

Therefore, the examiner hereby withdraws the rejection of claims 1-8 under 35 U.S.C. 103(a) as obvious over Ramsby et al. *Electrophoresis*. 1994 Feb;15(2):265-77. in view of Asada et al. *J. Enzym. Inhib*. 1989 3 (1), 49-56.

NEW GROUNDS OF REJECTION

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Henkart et al. (US-5,607,831, issued 4 Mar 1997) in view of Squier et al. (Journal of Cellular Physiology, May 1994; 159(2): 229-237) and further in view of Maki et al. (The Journal of Biological Chemistry, Nov.15, 1989; 264(32): 18866-18869) and further in view of Haake et al. (J Invest Dermatol, 1993; 101: 107-112).

Claim 1 is directed to a method for detecting an inhibitor of p53 protein degradation comprising providing a cell extract containing one or more p53 proteins and

one or more proteases, administering a peptide or protein inhibitor of calpain protease activity, and measuring p53 protein and p53 protein fragments.

Claim 2 is directed to the method of claim 1, wherein the inhibitor administered is a calpastatin.

Claim 3 is directed to the method of claim 2, wherein the calpastatin is encoded by one of SEQ ID NO: 1-3.

Claim 4 is directed to method of claim 1, wherein the cell extract is derived from a tumor cell.

Claim 6 is a method of claim 4, wherein the inhibitor is a calpastatin.

Claims 5 and 7 are directed to the methods of claims 1 and 4, respectively, wherein the inhibitor is a fragment of calpastatin.

Claim 8 is directed to the method of claim 1, wherein measuring the p53 protein and p53 protein fragments is performed using gel electrophoresis.

Henkart et al. teach "calpain has been identified as a component of the biochemical pathway in programmed cell death. Calpain inhibitors are effective in preventing the progression to cell death and can restore cell function....Methods for diagnosing cell populations or individuals susceptible to programmed cell death and for monitoring therapeutic effectiveness are provided." (abstract). Henkart et al. teach "a particularly useful calpain inhibitor is calpastatin and derivative thereof....synthetic oligopeptides, including on of 27 amino acids, which corresponds to a conserved region of calpastatin, have been prepared and found to regulate calpain activity" (col.7, lines

40-50). Henkart et al. measure DNA fragmentation by gel electrophoresis to determine apoptosis/programmed cell death.

Squier et al. teach, “calpain is necessary for triggering apoptosis” and “calpain inhibitors prevented apoptosis” (page 229, col.2). Squier et al. teach, “To discover how calpain may route a cell into the apoptotic pathway, known substrates of calpain which have also been implicated in apoptosis should be investigated.” (page 235, col.2, Effects of Calpain activation). Squier et al. also teach making cell extracts and performing Western blots (including electrophoresis) in order to test samples. Further, Squier et al. tested whether calpain played a role in apoptosis by administering Calpain Inhibitor 1 (i.e., peptide Ac-Leu-Leu-Nle-H) to thymocytes and observing cell morphology changes and DNA fragmentation (page 232, col.2). Furthermore, Squier et al. describe calpastatin as an endogenous inhibitor of calpain (page 235, col.1).

Squier et al. do not teach that p53 is a ligand of calpain. Squier et al. also do not teach that p53 is involved in apoptosis, although this was generally known in the art at the time Squier was published.

Maki et al. teach “calpastatin is a...endogenous inhibitor protein specifically acting on calpain" (abstract). Maki et al. also identify a “synthetic peptide showing strong inhibition against calpain I...[which is] a self-sufficient functional subdomain of the calpastatin inhibitory domain" (abstract). Maki et al. also supply the human sequence for calpastatin.

Maki et al. do not teach that p53 is a substrate of calpain or that p53 is involved in apoptosis.

Ramsby et al. teach, "two-dimensional (2-D) gel electrophoresis…used…to assess…protein…degradation" (page 265, Abstract). Ramsby et al. teach, "extraction of isolated hepatocytes" (page 268, col.1, Results and Discussion). Ramsby et al. teach "distribution of proteins in 2-D gels" including p53 protein (page 275). Ramsby et al. teach, use of EDTA which is "an effective inhibitor of the calcium-activated proteases, calpains I and II. These proteases, along with their endogenous inhibitor, calpastatin, are predominantly cytosolic proteins." (page 271, col.1, 2nd parag.). Ramsby et al. teach "distribution of proteins in 2-D gels" including p53 protein (page 275). In addition, Ramsby et al. teach that their method "is applicable to use with limited amounts of biomaterial and with other cell types or culture systems" (page 276, Conclusions), inferring that it is obvious to use their system with any cell extract, including tumor cell extracts.

Ramsby et al. does not specifically teach the limitations of claims 2, directed to the particular SEQ ID NO:1-3, and limitations of claims directed to tumor cell extracts and the limitations of claims directed to fragments of calpastatin.

In addition, the instant specification states, "Calpastatin is a known inhibitor of the calpains. Its sequence has been described in the prior art (SEQ ID No. 1)." (page 5, lines 22-24).

It would have been obvious to the person of ordinary skill in the art at the time of the invention was made to combine the teachings of Henkart et al. and Squier et al. and Maki et al. and Ramsby et al. and Haake et al. in a method for detecting an inhibitor of p53 protein degradation by administering a calpain protease.

The person of ordinary skill in the art would have been motivated to combine these references. While none of the above detailed references specifically indicate that p53 is a substrate of calpain, both are shown to be involved in the apoptotic pathway, particularly as are indicated by Henkart et al. and Squier et al. For further details about the relationship between p53 and apoptosis, see Haake et al. As the role of p53 is frequently examined when any new mechanistic understanding of cancer biology is undertaken, it is scientifically logical to measure the effect of calpain-calpastatin on p53 degradation.

Absent evidence to the contrary, an artisan would have expected success, because performing gel electrophoresis on cell extracts is well known.

Therefore the method as taught by Henkart et al. in view of Squier et al. and further in view of Maki et al. and further in view of Ramsby and further in view of Haake et al. would have been *prima facie* obvious over the method of the instant application.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SDL/ Scott Long Patent Examiner, Art Unit 1633	/Janet L. Epps-Ford/ Primary Examiner, Art Unit 1633